In re Application of: Peter ASSAF et al
Serial No.: 10/555,664
Filed: November 4, 2005
Office Action Mailing Date: January 4, 2008

Examiner: Sun Jae Y. Loewe
Group Art Unit: 1626
Attorney Docket: 30724

## REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-75 are in this case. Claims 2, 3, 7, 12-15, 18-27, 30, 31 and 34-64 have been withdrawn from further consideration as being drawn to a non-elected invention (claims 34-64) and non-elected species (claims 2, 3, 7, 12-15, 18-27, 30 and 31). Claims 1, 4-6, 8-11, 16, 17, 28, 29, 32, 33 and 65-75 have been examined on the merits with **Pet-12** as elected species. Claims 1, 4-6, 8-11, 16, 17, 28, 29, 32, 33 and 65-75 have been rejected.

Claims 1-5, 7-16 and 18-31 have been canceled herewith. Claims 6, 17, 32, 33 and 65 have been amended herewith.

### *Election/Restriction*

The Examiner has stated that although he finds the elected species Pet-12 not allowable under 35 U.S.C. 112, in the interest of expediting prosecution, non-elected species were rejoined and examined. The Examiner has therefore limited the scope of the search to compounds of Formula I, wherein:

X = pyridinyl (pyridine);

A = alkenyl, alkoxy, alkyl, alkynyl, amine, C-amide, carbonyl, C-carboxylate, cycloalkyl, diazo, disulfide, guanidine, guanyl, haloalkyl, hydrazine, N-amide, N-carbamate, nitro, O-carbamate, O-carboxylate, oxygen, sulfur, or absent; cyclic substituents (e.g, heteroaryl, aryl, aryloxy) limited to benzodioxole, diazole, piperidine, pyridine, thiazole, pyrazine, dithiolane, furan, thiophene, benzothiophene, pyrrolidine, quinoline, phenyl and naphthyl;

B = unsubstituted alkylene chain or unsubstituted alkylene interrupted by one heteroatom;

Y = $-ONO_2$; and

Z = hydrogen or unsubstituted alkyl.

The Examiner has stated that non-elected species outside of the subgenus defined above are patentably distinct and are not rejoined.

The Examiner has further stated that claims 2, 3, 7, 12-15, 18-27, 30-31 and 34-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being

drawn to a nonelected subject matter, and that Applicant timely traversed the restriction requirement between Groups I-VI in the response dated November 7, 2007.

Applicant wishes to note in this regard that as stated in the response to the Restriction Action dated October 9, 2007, the instant application is of compounds designed such that upon releasing NO, a thiamine-derived biocompatible metabolite is produced, thereby reducing the development of tolerance thereto upon repetitive administrations. These compounds were designed while considering the enzymatic mechanisms that lead to the release of bioactive NO, the development of tolerance to NO-donors and the decomposition of Vitamin $B_1$ (for detailed descriptions see, for example, from page 4 line 16 to page 7 line 2 and from page 29 line 16 to page 30 line 23 of the instant application).

These compounds therefore include, as illustrated in the general formula presented in claim 6 (see page 32, line 3 to page 33, line 20 of the instant application), a thiazole core, substituted at position 5 (adjacent to the sulfur atom) by an NO-releasing group (denoted as Y, see page 41, lines 4-13), via a spacer (denoted as B, see page 41, lines 18-32); substituted at position 4 (adjacent to the nitrogen atom, denoted as Z, see page 42. lines 5-11); and further substituted at position 2 (separating the nitrogen and sulfur atoms) by various moieties (denoted as X, see page 42, lines 12-26). The latter (X) can be linked directly to the thiazole core or indirectly, via a linking group (denoted as A, see page 48, line 30 to page 49, line 15).

***In view of the nature of the variables depicted in Formula I, and particularly in view of variable A being a linking moiety linking the X moiety to the thiazole core, Applicant respectfully believes that a search expanded beyond the elected species should include a subgenus with respect to the variable X and NOT with respect to the variable A, as chosen by the Examiner.***

Applicant wishes to note in this regard that in the Restriction Action dated October 9, 2007, the Examiner has identified Group I as reading on compounds/products of Formula I in which **A OR X** are alkenyl, alkoxy, alkyl, alkynyl, amine, C-amide, carbonyl, C-carboxylate, cycloalkyl, diazo, disulfide, guanidine, guanyl, haloalkyl, hydrazine, N-amide, N-carbamate, nitro, O-carbamate, O-carboxylate, oxygen, sulfur, or absent; cyclic substituents (e.g., heteroaryl, aryl,

aryloxy) limited to benzodioxole, diazole, piperidine, pyridine, thiazole, pyrazine, dithiolane, furan, thiophene, benzothiophene, pyrrolidine, quinoline, phenyl, naphthyl.

In the response to the Restriction Action, Applicant has noted that the elected species corresponds to Formula I in which ***A is absent and X is pyridine-3-yl.***

Applicant has therefore chosen to amend the claims so as to read on compounds having Formula I, in which X is a heteroaryl selected from the group consisting of benzodioxole, benzothiophene, diazole, dithiolane, furan, imidazole, indole, phthalazine, piperidine, pyrazine, pyrazole, pyridine, pyridinyl, pyrimidine, pyrrolidine, quinoline, thiadiazole, thiazole and thiophene.

While Applicant is aware of the search being conducted for X=pyridinyl, Applicant respectfully requests that when all the claims drawn to the elected subject matter are allowable, examination of the subgenus, as presently presented in the claims with respect to the variable X, will be effected. The Examiner's attention is also referred in this regard to the subsection below, entitled "Examination of generic claims".

***Priority***

The Examiner has acknowledged receipt of papers submitted under 35 U.S.C. 119(a)-(d).

Applicant wishes to draw the Examiner attention to several applications, having the Serial Nos. 11/266,346 (Attorney's Docket No. 30728); 11/266,424 (Attorney's Docket No. 30727); 11/266,431 (Attorney's Docket No. 30729); and 11/266,441 (Attorney's Docket No. 30730), which are members of the family of the instant application, and to the statement made by one of the Examiners prosecuting these applications, Ms. Laura L. Stockton, regarding the priority documents pertaining U.S. Patent Application Nos. 11/266,346, 11/266,424 and 11/266,431. It is noted that these priority documents are the same as the priority documents of the instant application.

The Examiner of U.S. Patent Application Nos. 11/266,346, 11/266,424 and 11/266,431 has stated that since these applications claim the benefit under 35 USC § 119(e) of Provisional Patent Application No. 60/567,824, filed May 5, 2004 and Provisional Patent Application No. 60/651,619, filed February 11, 2005, the

disclosures in both provisional applications were reviewed because of the possibility of intervening art. The Examiner in the above-referenced cases has further stated that it was found that Provisional Patent Application No. 60/651,619 fully supported the entire scope of these applications; however, Provisional Patent Application No. 60/567,824 fails to provide adequate support for the entire scope of these applications. The Examiner in the above-referenced cases has stated that only specie, not a genus as claimed, was found in Provisional Patent Application No. 60/567,824, and therefore, the claimed inventions can only rely on the filing date of Provisional Patent Application No. 60/651,619, which is February 11, 2005. The Examiner in the above-referenced cases has acknowledged that some species described and claimed in U.S. Patent Application Nos. 11266/,346, 11/266,424 and 11/266,431 were found in Provisional application 60/567,824.

In this regard Applicant argued and contends that the concept of designing unique NO-releasing compounds that upon NO release produce a biocompatible thiamine-derived residue, as delineated hereinabove, is well described in Provisional Patent Application No. 60/567,824, and that to this effect, the design and preparation of dozens of thiazole-based NO-releasing compounds is described in detail therein (see, page 4, line 1 to page 6, line 10 in application having Serial No. 11/266,346). Thus, a genus is described in the Provisional Patent Application No. 60/567,824 while describing compounds that are designed such that upon administration, these compounds are subjected to enzymatic reactions that release a bioactive NO, and form a residue which is derived from a naturally occurring metabolite, preferably being a residue of vitamin B (thiamine). Provisional Patent Application No. 60/567,824 also provides descriptions of subgenus groups defined by the substituents that are attached to the thiazole-based residue at position 2 thereof, including a subgenus wherein the thiazole moiety is substituted with an alkyl, a subgenus wherein the thiazole moiety is substituted with an alkyl, and a subgenus wherein the thiazole moiety is substituted with a NO-releasing moiety, which represent the claimed subject matter in the above-referenced U.S. Patent Applications.

Applicant therefore respectfully submits that while the general concept of thiamine-based NO-releasing compounds is fully described in Provisional Patent Application No. 60/567,824 and further while dozens of species embraced by claim 1

of the instant application and moreover by the general formula in claim 6 of the instant application are presented in Provisional Patent Application No. 60/567,824 as representative examples of the NO-donating compounds described in the instant application, Provisional Patent Application No. 60/567,824 provides ample grounds for the claimed priority of the instant application effective May 5, 2004.

***Claim objections***

The Examiner has stated that claims 1, 4-6, 8-11, 16, 17, 28, 29, 32, 33 and 65-75 are objected to for containing non-elected subject matter.

Claims 1, 4, 5, 8-11, 16, 28 and 29 have been canceled herewith. Claims 2, 3, 7, 12-25, 18-27, 30 and 31 have also been canceled herewith. Claims 6, 17, 32, 33 and 65 have been amended herewith.

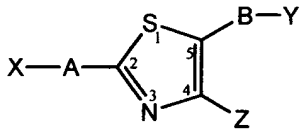
As argued hereinabove, Applicant strongly believes that a subgenus relevant to the instant application should read on compounds having Formula I, in which X is a heteroaryl.

Applicant has therefore chosen to amend the claims so as to read on the elected subject matter, as indicated by the Examiner, while reciting additional heteroaryl moieties with respect to the variable X.

Applicant has further chosen, in order to expedite prosecution, to cancel claims currently drawn to non-elected species.

Hence, claims 1-5 have now been canceled, and claim 6 has now been amended so as to recite:

*~~The~~ An NO-donating compound ~~of claim 5,~~ having the general formula I:*




*Formula I*

*wherein:*

*A is selected from the group consisting of ~~alkenyl, alkoxy,~~ alkyl, ~~alkynyl,~~ amine, ~~amine oxide,~~ aryl, ~~aryloxy, azo, borate,~~ C-amide,*

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*carbonyl, ~~C-carboxylate, C-thiocarboxylate, cycloalkyl, diazo, disulfide, guanidine, guanyl, haloalkyl, heteroalicyclic, heteroaryl,~~ hydrazine, N-amide, ~~N-carbamate, N-dithiocarbamate, nitro, N-sulfonamide, N-thiocarbamate, O-carbamate, O-carboxylate, O-thiocarbamate, O-thiocarboxylate, oxime, oxygen, sulfur, peroxo, phosphate, phosphine oxide, phosphine sulfide, phosphinyl, phosphite, phosphonate, pyrophosphate, S-dithiocarbamate, silaza, silicate, siloxy, silyl, S-sulfonamide, sulfate, sulfite, sulfonate, sulfoxide, sulfur, thioalkoxy, thioaryloxy, thiocarbonyl, thiophosphate, thiosulfate, thiosulfite, thiourea, triphosphate, urea, a biocleavable moiety~~ and any combination thereof, or absent;*

*X is ~~selected from the group consisting of acyl halide, alkenyl, alkoxy, alkyl, alkynyl, amine, amine oxide, aryl, aryloxy, azo, borate, C-amide, carbonyl, C-carboxylate, C-thiocarboxylate, cyano, cycloalkyl, diazo, disulfide, guanidine, guanyl, halide, haloalkyl, heteroalicyclic, a~~ heteroaryl selected from the group consisting of benzodioxole, benzothiophene, diazole, dithiolane, furan, imidazole, indole, phthalazine, piperidine, pyrazine, pyrazole, pyridine, pyridinyl, pyrimidine, pyrrolidine, quinoline, thiadiazole, thiazole and thiophene, ~~hydrazine, hydrogen, hydroxy, N-amide, N-carbamate, N-dithiocarbamate, nitro, N-sulfonamide, N-thiocarbamate, O-carbamate, O-carboxylate, O-thiocarbamate, O-thiocarboxylate, oxime, peroxo, phosphate, phosphine oxide, phosphine sulfide, phosphinyl, phosphite, phosphonate, pyrophosphate, S-dithiocarbamate, silaza, silicate, siloxy, silyl, S-sulfonamide, sulfate, sulfite, sulfonate, sulfoxide, thioalkoxy, thioaryloxy, thiocarbonyl, thiohydroxy, thiophosphate, thiosulfate, thiosulfite, thiourea, triphosphate, urea, a bioactive agent residue, a moiety containing at least one NO releasing group, a substituted or unsubstituted thiazole and any combination thereof;*

*B is an ethylene chain ~~selected from the group consisting of a saturated or unsaturated, substituted or unsubstituted alkylene chain having 1-20 carbon atoms, and a saturated or unsaturated, substituted~~*

~~*or unsubstituted alkylene chain having 1-20 carbon atoms interrupted by at least one heteroatom, whereby said at least one heteroatom comprises oxygen, sulfur, nitrogen, phosphor, silicon and any combination thereof;*~~

*Y is* $-ONO_2$ ~~*said NO-releasing group*~~*; and*

*Z is methyl* ~~*selected from the group consisting of hydrogen and alkyl, alkenyl, alkynyl, amine, cycloalkyl, heteroalicyclic, aryl, heteroaryl, halide, haloalkyl, hydroxy, thiohydroxy, alkoxy, thioalkoxy, aryloxy and thioaryloxy;*

*the compound being such that when NO is released from the compound a residue which is a naturally occurring metabolite is formed, thereby decreasing a development of tolerance to the NO-donating compound upon repetitive administration thereof.*

Consequently, claims 8-11, 16, 28 and 29 have been canceled. Claims 7, 12-15, 18-27, 30 and 31 have also been canceled.

Claim 17 has been amended so as to recite a particular selection of one possible moiety pertaining to variable X of Formula I and to depend from claim 6. Claim 32 has been amended so as to read on a selection of exemplary embodiments of compounds according to claim 6 (Formula I), and claims 33 and 65 have been amended so as to depend from claim 6.

Applicant believes to have overcome the Examiner's objection.

***35 U.S.C. § 112 First Paragraph Rejections – Written description***

The Examiner has stated that claims 1, 4-6, 8-11, 16, 17, 28, 29, 33 and 65-75 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The Examiner's rejection is respectfully traversed.

Claims 1, 4, 5, 8-11, 16, 28 and 29 have been canceled herewith. Claims 2, 3, 7, 12-25, 18-27, 30 and 31 have also been canceled herewith. Claims 6, 17, 32, 33 and 65 have been amended herewith.

Generally, the Examiner has alleged that (i) substantial structural variation exists in the genus/subgenus embraced by claims 1, 4-6, 8-11, 16, 17, 28, 29, 33 and 65-75; (ii) disclosure of species supporting genus is limited to compounds reduced to

practice, which scope is not commensurate with the scope of genus/subgenus claimed; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art, and thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Specifically, the Examiner has stated that for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim, and that the MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus.

As argued hereinabove, the present invention is of NO-releasing compounds that were designed such that upon entering a biological system, a bioactive NO would be released and a residue of a naturally occurring metabolite (e.g., Vitamin $B_1$) would be formed, whereby the formation of such a metabolite would prevent or decrease the development of tolerance to these compounds. The claimed genus, as presented in the instant application, therefore includes a thiazole core, substituted at position 5 (adjacent to the sulfur atom, see Formula I) by an NO-releasing group, via a spacer; substituted at position 4; and further substituted at position 2 by various moieties which can be linked directly to the thiazole core or indirectly, via a linking group. The structural feature of the genus is widely and clearly described and defined in the instant application, as presented hereinabove with precise references in the instant application per each of the variables in Formula I.

Applicant contends that in terms of written description requirements, the instant specification provides ample support for the desired structural features of each and every variable in Formula I.

*I. Scope of Claims based on searched and examined subject matter*:

The Examiner has stated that when the structural limitations, defined by the Examiner in the present office action, are applied to the compounds of Formula I, the following variables are claimed broader than what is supported by the disclosure:

Variable B: for all claims except claims 10, 11, 16 and 17;

Variable A: for all claims.

As delineated hereinabove, Applicant strongly believes that the definitions of variables A and B are fully supported by the description.

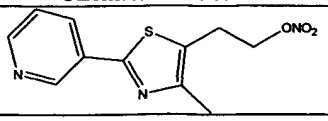
Notwithstanding the above, Applicant has chosen, in order to expedite prosecution, to amend the claimed invention so as read on compounds having Formula I as presented in claim 6, in which B is an ethylene chain and A is selected from the group consisting of alkyl, amine, aryl, C-amide, carbonyl, hydrazine, N-amide and any combination thereof, or absent.

The Examiner's attention is directed, for example, to Tables 1 and 2 of the instant application, in which dozens of compounds in which B is an ethylene chain are presented.

The Examiner's attention is further directed to the following compounds in Tables 1 and 2, in which **X** is a heteroaryl such as 1,2,3-thiadiazole-4-yl, 1,4-dioxide-pyrazine-2-yl, 1H-imidazol-5-yl-4-amine, *1H*-indole-3-yl, 1-oxide-3-pyridyl, 1-oxide-pyrazine-3-yl, 2-(trifluoromethyl)pyridine-5-yl 1-oxide, 2-chloro-6-(trifluoromethyl)-3-pyridyl, 2-ethyl-pyridine-4-yl 1-oxide, 2-ethyl-pyridine-5-yl, 2-methylpyrimidin-4-amine-5-yl, 3,5-dimethyl-1H-pyrazole-1-yl, 3-pyridyl, 4-(diethylamino)pyridin-3-yl, 4-pyridyl, 6-(methylamino)pyrazin-2-yl, 6-(trifluoromethyl)pyridin-3-yl, 6-methoxypyrazin-2-yl, 6-methylpyridin-3-yl, benzo[b]thiophene-2-yl, furan-2-yl, phthalazine-1-yl, pyrazine-2-yl and thiophen-2-yl;

and wherein **A** is amine, C-amide, N-amide, hydrazine, ethane-1,1-diyl, methylene, methanone (carbonyl, oxomethylene), methylamine (amine and methylene), nitrooxy-methylene and phenyl (aryl).

In order to clarify and substantiate the above arguments, Applicant consolidated the structural and chemical information regarding the presently claimed subgenus, as defined by the Examiner, in the table presented below.

| Compound | Chemical Structure | Variable A | Variable X |
|---|---|---|---|
| **Pet-12** |  | Absent | 3-pyridyl |

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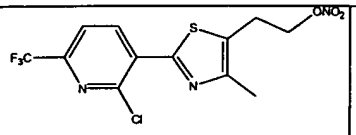
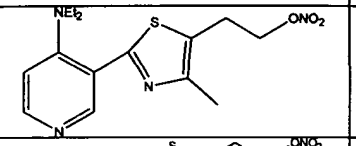
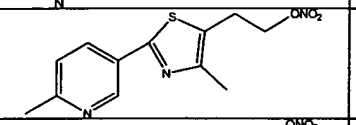
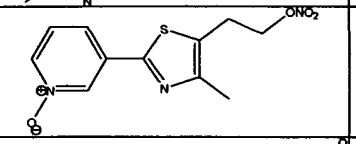
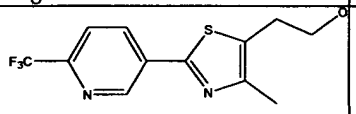
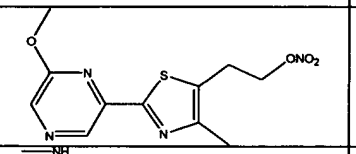
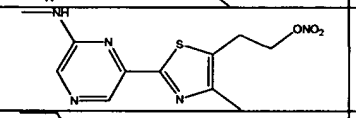
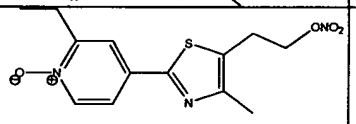
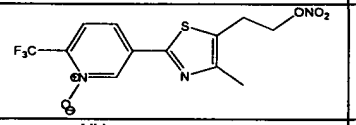
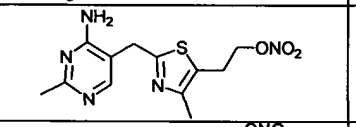
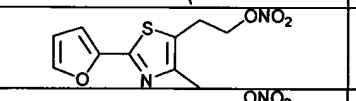
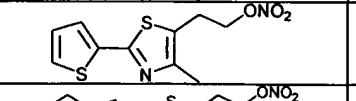
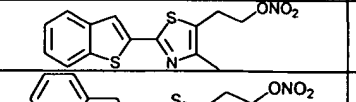
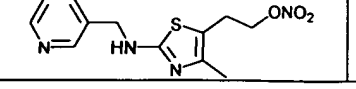
| | | | |
|---|---|---|---|
| **Pet-18** |  | Absent | 2-chloro-6-(trifluoromethyl)-3-pyridyl |
| **Pet-19** |  | Absent | 4-(diethylamino)pyridin-3-yl |
| **Pet-20** |  | Absent | 6-methylpyridin-3-yl |
| **Pet-21** |  | Absent | 3-pyridyl 1-oxide |
| **Pet-22** |  | Absent | 6-(trifluoromethyl)pyridin-3-yl |
| **Pet-23** |  | Absent | 6-methoxypyrazin-2-yl |
| **Pet-24** |  | Absent | 6-(methylamino)pyrazin-2-yl |
| **Pet-25** |  | Absent | 2-ethyl-pyridine-4-yl 1-oxide |
| **Pet-26** |  | Absent | 2-(trifluoromethyl)pyridine-5-yl 1-oxide |
| **Pet-68** |  | methylene | 2-methylpyrimidin-4-amine-5-yl |
| **Pet-69** |  | Absent | furan-2-yl |
| **Pet-71** |  | Absent | thiophen-2-yl |
| **Pet-72** |  | Absent | benzo[b]thiophene-2-yl |
| **Pet-80** |  | methylamine (amine and methylene) | 3-pyridyl |

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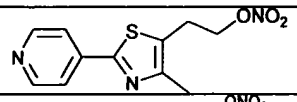
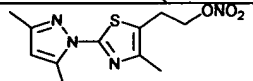
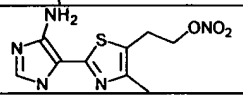
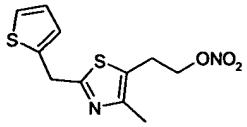
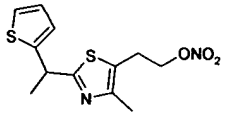
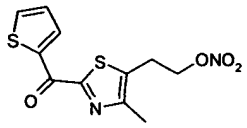
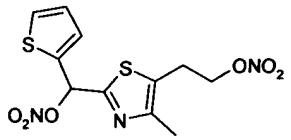
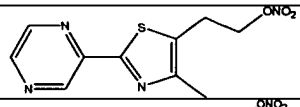
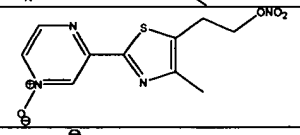
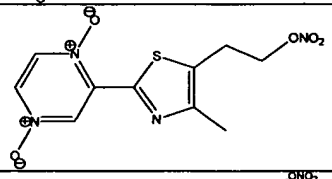
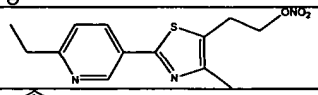
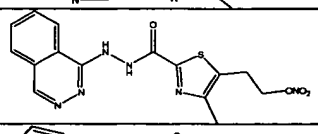
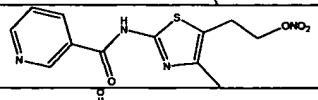
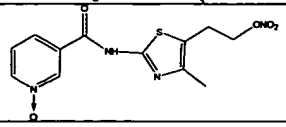
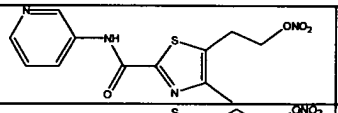
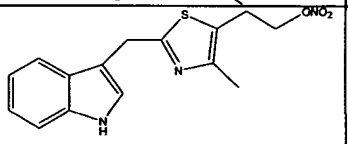
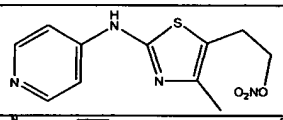
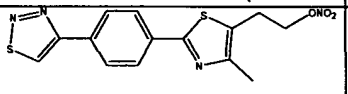
|---|---|---|---|
| **Pet-81** |  | Absent | 4-pyridyl |
| **Pet-83** |  | Absent | 3,5-dimethyl-1H-pyrazole-1-yl |
| **Pet-84** |  | Absent | 1H-imidazol-5-yl-4-amine |
| **Pet-86** |  | methylene | thiophen-2-yl |
| **Pet-87** |  | ethane-1,1-diyl | thiophen-2-yl |
| **Pet-88** |  | methanone (carbonyl, oxomethylene) | thiophen-2-yl |
| **Pet-95** |  | nitrooxy-methylene | thiophen-2-yl |
| **Pet-125** |  | Absent | pyrazine-2-yl |
| **Pet-126** |  | Absent | pyrazine-3-yl 1-oxide |
| **Pet-127** |  | Absent | pyrazine-2-yl 1,4-dioxide |
| **Pet-144** |  | Absent | 2-ethyl-pyridine-5-yl |
| **Pet-153** |  | C-hydrazide (carbonyl and hydrazine) | phthalazine-1-yl |
| **Pet-154** |  | N-amide | 3-pyridyl |
| **Pet-156** |  | N-amide | 3-pyridyl 1-oxide |

| | | | |
|---|---|---|---|
| **Pet-170** |  | C-amide | 3-pyridyl |
| **Pet-172** |  | methylene | *1H*-indole-3-yl |
| **Pet-174** |  | amine | 4-pyridyl |
| **Pet-178** |  | phenyl (aryl) | 1,2,3-thiadiazole-4-yl |

Applicant therefore strongly believes that the instant specification clearly indicates that Applicant has demonstrated possession of the claimed invention in its generic context, let alone of the compounds encompassed by the claimed general Formula I (see, claim 6).

*II. Scope of disclosure – reduction to practice; and reduction to structural or chemical Formulae*)

The Examiner has stated that the compounds reduced to practice support the following definitions for the variables noted above, namely:

Variable B: unsubstituted alkylene chain

Variable A: absent, amide, amine, alkylene-amine (based on methylene amine).

The Examiner has further stated that the only disclosure, in addition to the species reduced to practice, is in form of lists of possible group (e.g. pyrrole, furane, thiophene, imidazole, oxazole, thiazole, pyrazole and pyridine for heteroaryl), that this type of disclosure is not a representation of any of the species it entails, and that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species, and therefore there is no disclosure of species (e.g. by reduction to structural/chemical formulas) in addition to those reduced to practice.

As argued hereinabove, Applicant contends that in terms of written description requirements, the instant specification provides ample support for the desired

structural features of each and every variable in Formula I, including variables B, A and X.

Notwithstanding the above, Applicant has chosen, in order to expedite prosecution, to amend the claimed invention so as read on compounds having Formula I as presented in claim 6, in which B is an ethylene chain and A is selected from the group consisting of alkyl, amine, aryl, C-amide, carbonyl, hydrazine, N-amide and any combination thereof, or absent.

Applicant wishes to refer to MPEP § 2163, cited by the Examiner, which specifically states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus and that of the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus.

The instant disclosure describes 185 species that encompass the genus (see, for example, Tables 1 and 2), and 14 species that encompass the subgenus defined by the Examiner in Section 4 of the instant Action. The latter includes the following species: 3-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazole-2-yl]-pyridine (**Pet-12**), 2-Chloro-3-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-6-trifluoromethyl-pyridine (**Pet-18**), Diethyl-{3-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridin-4-yl}-amine (**Pet-19**), 2-Methyl-5-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine (**Pet-20**), 3-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine 1-oxide (**Pet-21**), 5-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-2-trifluoromethyl-pyridine (**Pet-22**), 2-Methoxy-6-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyrazine (**Pet-23**), 2-Ethyl-4-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine 1-oxide (**Pet-25**), 5-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-2-trifluoromethyl-pyridine 1-oxide (**Pet-26**), [4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine (**Pe-80**), 4-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine (**Pet-81**), 2-Ethyl-5-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine (**Pet-144**), 4-Methyl-5-(2-nitrooxy-ethyl)-thiazole-2-carboxylic acid pyridin-3-ylamide (**Pet-170**) and [4-Methyl-5-(2-nitrooxy-ethyl)-2-yl]-pyridin-4-yl-amine (**Pet-174**).

The instant disclosure also describes 33 species that encompass a subgenus in which X is a heteroaryl selected from the group consisting of benzodioxole, benzothiophene, diazole, dithiolane, furan, imidazole, indole, phthalazine, piperidine,

pyrazine, pyrazole, pyridine, pyridinyl, pyrimidine, pyrrolidine, quinoline, thiadiazole, thiazole and thiophene, including the following: 3-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazole-2-yl]-pyridine (**Pet-12**); 2-Chloro-3-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-6-trifluoromethyl-pyridine (**Pet-18**); Diethyl-{3-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridin-4-yl}-amine (**Pet-19**); 2-Methyl-5-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine (**Pet-20**); 3-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine 1-oxide (**Pet-21**); 5-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-2-trifluoromethyl-pyridine (**Pet-22**); 2-Methoxy-6-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyrazine (**Pet-23**); Methyl-{6-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyrazin-2-yl}-amine (**Pet-24**); 2-Ethyl-4-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine 1-oxide (**Pet-25**); 5-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-2-trifluoromethyl-pyridine 1-oxide (**Pet-26**); 3-(4-Amino-2-methyl-pyrimidin-5-ylmethyl)-4-methyl-5-(2-nitrooxy-ethyl)-thiazol-3-ium; chloride (**Pet-68**); 2-Furan-2-yl-4-methyl-5-(2-nitrooxy-ethyl)-thiazole (**Pet-69**); 4-Methyl-5-(2-nitrooxy-ethyl)-2-thiophen-2-yl-thiazole (**Pet-71**); 2-Benzo[b]thiophen-2-yl-4-methyl-5-(2-nitrooxy-ethyl)-thiazole (**Pet-72**); [4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridin-3-ylmethyl-amine (**Pe-80**); 4-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine (**Pet-81**); 2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-5-(2-nitrooxy-ethyl)-thiazole (**Pet-83**); 5-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-1H-imidazol-4-ylamine (**Pet-84**); 4-Methyl-5-(2-nitrooxy-ethyl)-2-thiophen-2-ylmethyl-thiazole (**Pet-86**); 4-Methyl-5-(2-nitrooxy-ethyl)-2-(1-thiophen-2-yl-ethyl)-thiazole (**Pet-87**); [4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-thiophen-2-yl-methanone (**Pet-88**); 4-Methyl-5-(2-nitrooxy-ethyl)-2-(nitrooxy-thiophen-2-yl-methyl)-thiazole (**Pet-95**); 2-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyrazine (**Pet-125**); 2-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyrazine 4-oxide (**Pet-126**); 2-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyrazine 1,4-dioxide (**Pet-127**); 2-Ethyl-5-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-pyridine (**Pet-144**); 4-Methyl-5-(2-nitrooxy-ethyl)-thiazole-2-carboxylic acid N'-phthalazin-1-yl-hydrazide (**Pet-153**); N-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-nicotinamide (**Pet-154**); N-[4-methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-1-oxy-nicotinamide (**Pet-156**); 4-Methyl-5-(2-nitrooxy-ethyl)-thiazole-2-carboxylic acid pyridin-3-ylamide (**Pet-170**); 3-[4-Methyl-5-(2-nitrooxy-ethyl)thiazol-2-ylmethyl]-1H-indole (**Pet-172**); [4-Methyl-5-(2-nitrooxy-ethyl)-2-yl]-pyridin-4-yl-amine (**Pet-**

In re Application of: Peter ASSAF et al
Serial No.: 10/555,664
Filed: November 4, 2005
Office Action Mailing Date: January 4, 2008

Examiner: Sun Jae Y. Loewe
Group Art Unit: 1626
Attorney Docket: 30724

**174**); and 4-{4-[4-Methyl-5-(2-nitrooxy-ethyl)-thiazol-2-yl]-phenyl}-[1,2,3]thiadiazole (**Pet-178**).

Applicant therefore strongly believes that the number of representative species that are specifically described by their exact chemical structure and which encompass the genus and the examined subgenus is more than sufficient in order to adequately describe the claimed invention, in accordance with MPEP § 2163.

Applicant further contends that patent applicants are not required to disclose every species encompassed by their claims. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

*II. Scope of disclosure* – correlation between structure and function:

The Examiner has stated that the correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification, and thus, it is not understood what specific structural elements allow for preservation of the claimed activity in compounds within the unrepresented genus.

As argued hereinabove, the compounds described in the instant application were designed after a well-defined concept and therefore include structural features that are in line with this concept. The correlation between those structural and functional features of each and every variable in Formula I (see, page 32, line 3 to page 33, line 20 of the instant application) are, as argued hereinabove, clearly described in the instant application. Thus, the functional features of the NO-releasing group, denoted as Y (see page 41, lines 4-13), of the spacer, denoted as B (see page 41, lines 18-32), the substituent at position 4 on the thiazole, denoted as Z (see page 42. lines 5-11), the substituent at position 2, denoted as X (see page 42, lines 12-26), and the linking group denoted as A (see page 48, line 30 to page 49, line 15) are described.

Notably, a main structural feature of the claimed compounds is the presence of a thiazole core, substituted at a certain position by a moiety that includes an NO-releasing group. Such a thiazole core is presented in the claimed Formula I for the genus and any subgenus altogether.

The effect of 11 species encompassed by the genus and of 3 species encompassed by the subgenus defined by the Examiner in Section 4 of the instant

Action in decreasing tolerance to known NO releasing compounds, has been demonstrated (see, page 146, line 16 to page 147, line 14 of the instant application).

The effect of 3 species that encompass a subgenus in which X is a heteroaryl selected from the group consisting of pyridine, pyrazine and a 3-pyridyl linked via an N-amide, in decreasing tolerance to known NO releasing compounds, has been demonstrated (see, page 146, line 16 to page 147, line 14 in the instant application).

These results clearly establish the role of the thiazole-based, thiamine-derived core of the claimed genus in exhibiting the desired activity.

Applicant therefore contends that the instant application clearly describes structural elements that allow for preservation of the claimed activity in compounds within the genus and the claimed subgenus.

*III. Analysis of fulfillment of written description requirement*:

The Examiner has stated that the structure/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC50 and/or EC50 data of multiple compounds with various types of structural modifications, and that these types of studies provide insight into the structural limitations that are required for activity, i.e. specific structural elements essential for the claimed activity. The Examiner has further alleged that in the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

As argued hereinabove, Applicant contends that the instant application clearly describes structural elements that allow for preservation of the claimed activity in compounds within the genus and further demonstrates the preservation of the desired activity upon modification of the substituents represented by the variables A and/or X.

The Examiner's attention is directed in this regard to the Examples section of the instant application, where an activity of compounds sharing the above-mentioned thiazole core, and varying in the substituent at position 2 of the thiazole ring, which substituents correspond to variables A and X in Formula I, is demonstrated. These results clearly demonstrate that a sufficient number of representative species that encompass the genus, with various structural modifications in variables A and X, show preservation of the desired activity.

In view of the above, Applicant strongly believes that the specification provides adequate written description of the claimed genus, let alone the subgenus

defined by the Examiner in the instant Action and any other described subgenus, so as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, has possession of the entire scope of the claimed invention.

The Examiner attention is kindly drawn to the specification of the instant application, where no less than 33 species are presented to exemplify the concept and the genus they represent. Specifically, Applicant contends that by providing 33 examples, namely Pet-12, Pet-18, Pet-19, Pet-20, Pet-21, Pet-22, Pet-23, Pet-24, Pet-25, Pet-26, Pet-68, Pet-69, Pet-71, Pet-72, Pet-80, Pet-81, Pet-83, Pet-84, Pet-86, Pet-87, Pet-88, Pet-95, Pet-125, Pet-126, Pet-127, Pet-144, Pet-153, Pet-154, Pet-156, Pet-170, Pet-172, Pet-174 and Pet-178, (see, for example, Tables 1 and 2 in the instant application), the disclosure provides a sufficient variety of species to reflect the variation within the claimed genus.

While Applicant is of the opinion that the claimed genus and subgenus thereof is fully described in the specification of the instant application, Applicant has chosen to amend the claims so as to read on a certain subgenus, as detailed hereinabove. As argued hereinabove, Applicant strongly believes that the claimed subgenus is fully described in the instant specification.

Applicant therefore strongly believes to have overcome the Examiner's rejection.

***35 U.S.C. § 112 First Paragraph Rejections - Enablement***

The Examiner has stated that claims 1, 4-6, 8-11, 16, 17, 28, 29, 32, 33 and 65-75 are rejected under 35 U.S.C. 112, first paragraph, for failing to meet the enablement requirements. The Examiner's rejection is respectfully traversed.

Claims 1, 4, 5, 8-11, 16, 28 and 29 have been canceled herewith. Claims 2, 3, 7, 12-25, 18-27, 30 and 31 have also been canceled herewith. Claims 6, 17, 32, 33 and 65 have been amended herewith.

Specifically, the Examiner has stated that the specification <u>is enabling</u> for:

a) The intended use of "decreasing a development of tolerance to the NO-donating compound" (see pages 6, 7 and 148);

b) Making/using compounds that have written description support in the disclosure (see, Section 9.*II.* of the present office action),

and that the specification is not enabling for:

aa) The intended use of "Preventing a development of tolerance to the NO-donating compound";

bb) Using compounds that do not have written description support in the disclosure (see, Section 9.*II.* of the present office action).

The Examiner has further stated that the specification does not enable one of ordinary skill in the art to practice the invention commensurate in scope with the claims.

Applicant notes herein that drug tolerance is a complex and multifaceted biological phenomenon which can be identified and assessed only qualitatively. If a drug is found not to induce tolerance, it can be regarded as a drug that prevents the emergence of tolerance, and if this drug is used in combination of tolerance-inducing drugs, it will decrease the tolerance problem. Furthermore, in most cases, one cannot differentiate between the prevention and the decrement of emergence of drug tolerance in the context of biological NO-releasing mechanisms due to mixed mechanisms of manifestation of the problem. A skilled artisan is versed in the way drug tolerance emerges and suppressed, thus prevention and decrement are all but equivalent for such artisan.

Notwithstanding the above, claim 1, which recited the limitation "*[...] preventing or decreasing a development of tolerance [...]*" has now been canceled, thereby rendering moot the Examiner's rejection with respect thereto.

Claim 6 has been amended so as to recite "*[...] the compound being such that when NO is released from the compound a residue which is a naturally occurring metabolite is formed, thereby decreasing a development of tolerance to the NO-donating compound upon repetitive administration thereof.*".

The Examiner has further stated that the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270(1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable, and that this standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8USPQ2s 1400, 1404 (Fed. Cir. 1988).

Specifically, the Examiner has applied these factors to the instant claims

below:

*The breadth of the claims:*

aa) The Examiner has referred in this regard to compounds not supported by the disclosure (see Section 9.*I.* and 9.*II.* in the present office action).

bb) The Examiner has further referred to the claimed intended use: NO-donating compounds that prevent a development of tolerance to the NO-donating compound.

*The nature of the invention:*

aa) The Examiner has stated in this regard that the compounds are disclosed to be nitric oxide donors, and that an alternate utility is neither disclosed in the specification nor known in the art for this genus of compounds.

bb) The Examiner has alleged that "the specification discloses *in vitro* studies that show that the activity (based on measured cGMP levels) of the instantly claimed compounds in pre-infused aortic tissue is not significantly different (from) the activity in post-infused aortic tissue".

*The state of the prior art/level of ordinary skill/level of predictability:*

aa) The Examiner has alleged that the level of ordinary skill is high, but the level of predictability in the art is low, and that limited SAR is reported for the instantly claimed genus of compounds (i.e. subgenus defined in Section 4 of the present office action) – see, specification pages 143-151. The Examiner has further alleged that SAR studies have been disclosed for other compounds that have the same utility as instantly claimed.

The Examiner has further stated that as discussed in Section 9 of the present office action, it is not known what structural limitations are required for preservation of activity within the unrepresented genus, and that in view of the low level of predictability, as evidenced by the examples above, one of ordinary skill would not know what structural modifications would lead to compounds that have the claimed activity, and that the level of predictability in modulating tolerance is low. The Examiner has noted the following to demonstrate the state of the art:

- Multiple mechanisms underlie time- and dose-dependent tolerance (see, instant specification on page 6);
- Drug tolerance presents the most challenging limit for the clinical use

of organic nitrite and nitrate esters (see, instant specification page 5);

- Nitrate tolerance induced by the administration of nitroglycerin (an NO donor) is observed in situations where nitroglycerin is administered long term *in vivo* and is not induced by short-term exposure of vascular segments in vitro (see, page 1103 in Münzel, T., "Does nitroglycerin therapy hit the endothelium?", *J. Am. Coll. Cardiol.*, 2001, 38, 1102-1105).

The Examiner has further stated that the instant specification provides support for *in vivo* short term induced tolerance, and that these studies, in view of the low level of predictability, are not indicative to prevention of a development of tolerance – i.e. one set of experimental conditions is not indicative of all experimental conditions (as encompassed by the term "prevent").

*The amount of direction provided by the inventor/existence of working examples:*

aa) The Examiner has alleged that the direction and working examples are limited to the making/using of compounds that have written description support (see Section 9.*II.* of the present office action).

bb) The Examiner has alleged that the direction/guidance is limited and cannot be extended to support the full scope of claim supra.

*The quantity of experimentation needed to make or use the invention:*

aa) The Examiner has alleged that it is not known which of the unrepresented compounds meet the structural requirements for activity, and thus, one of ordinary skill would not be enabled by the disclosure to make/use the claimed NO-donors. The Examiner has further stated that the amount of experimentation needed to practice the invention commensurate in scope with the claims is undue, and further, absent an alternate utility, one of ordinary skill would not be enabled to use the compounds within the genus that are not adequately supported.

bb) The Examiner has alleged that in view of the low level of predictability, one of ordinary skill is not enabled by the instant disclosure to practice the invention commensurate in scope with the claims.

***Legal Standard***

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art

could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g., Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S,* 108 F.3d 1361, 42 USPQ2D 1004 (Fed. Cir. 1997) (quoting *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). *See also In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); *United States v. Telectronics, Inc.,* 857 F.2d 778 (Fed. Cir. 1988); *and In re Stephens,* 529 F.2d 1343, 188 USPQ 659 (CCPA 1976).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.LT. v. A.B. Fortia, 11A* F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.,* 323 F3d 956, 965-966, 63 USPQ2d 1609, 1614 (Fed. Cir. 2002).

In addition, a patent need not teach, and preferably omits, what is well known in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *citing Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.,* 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Thus, information that is conventional or well-known to one of ordinary skill in the art need not be disclosed by the specification.

The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.,* 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

Further, as previously argued by Applicant hereinabove, patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

***Analysis***

As detailed above, the test for enablement is whether one of ordinary skill in the art could make and use the claimed compositions and methods without undue experimentation. There is no requirement that all embodiments within a genus be

enabled to meet the standard for enablement.

Specifically, Applicant contends again that a synthetic method, which is applicable for all claimed compounds, was established for dozens of compounds and hence any a skilled artisan would be able to prepare and practice all the compounds within the genus, even those not specifically described.

Furthermore, Applicant contends that the Structure-Activity-Relationship (SAR) studies, which are reported in great details in the instant application, demonstrate the rationale behind the invention clearly by showing activity of the tested compounds, and moreover, by showing activity of compounds having the same core structure but various substituents. This thorough SAR report establishes features that are applicable for the claimed genus and any subgenus thereof.

A more detailed analysis of the *Wands* factors which follows clearly shows that the claimed NO-releasing compounds and compositions and methods utilizing the same are enabled. As discussed in detail below, based on the amount of guidance provided in the specification, the quantity of experimentation necessary, the presence of working examples, and the breadth of the claims, one of ordinary skill in the art would be able to make and use the claimed compounds, compositions and methods without undue experimentation.

*The breadth of the claims:*

Applicant contends that the scope of the invention, as compared to the task it attempts to accomplish, namely to provide a novel family of NO-donating compounds devoid of the limitations of the presently known NO-donating agents, is accurately defined as compounds having the structural features that are required, according to the rationale and experimental data set forth in the instant application, to provide the desired activity (see, amended claim 6 and arguments presented hereinabove).

*The nature of the invention:*

The Examiner has alleged that the compounds are disclosed to be nitric oxide donors, and that an alternate utility is neither disclosed in the specification nor known in the art for this genus of compounds. Further, the Examiner has alleged that the specification discloses *in vitro* studies that show that the activity (based on measured cGMP levels) of the instantly claimed compounds in pre-infused aortic tissue is not significantly different the activity in post-infused aortic tissue.

The specification, as presented in the instant application, is directed at a genus of compounds comprising a core structure based on a naturally occurring metabolite and an NO-donating moiety, and to use thereof as NO-level modulators.

The instant application teaches the utilization of a thiazole core which is shared by thiamin (vitamin $B_1$ or 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium) in the construction of highly efficacious NO-donating agents, designed according to an empirical paradigm of thiamin enzymatic metabolism process which triggers the release on nitric oxide. This rudimentary rational is presented, for example, on page 29, line 20 through page 31, line 17 of the instant application.

This seminal, vast, comprehensive and thorough study is described in details in the instant application, using the most accepted and acknowledged techniques and methods for testing, and analyzing both positive and negative results using the most approved comprehensive tools, standards and criteria known in the field.

The Examiner may have misunderstood the meaning of the results, as summarized in Table 5 in the instant application, presented so as to show **lack** of tolerance induction by the claimed compounds. These results show clearly that while the c-GMP level was significantly reduced following a repeated treatment with nitroglycerin (GTN), it remained almost unchanged following a repeated treatment with each of the tested NO-donors of the present invention, thus showing the **lack** of tolerance induction thereby, which is the intended goal to be achieved by the claimed compounds.

*The state of the prior art/level of ordinary skill/level of predictability:*

The relative skill of those in the art is high. As argued hereinabove, the unpredictability of the art does not preclude enablement, *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The coupling of the above-mentioned chemical moieties into an NO-donating compound is performed according to procedures which are more than amply detailed in the disclosure and are based on chemical synthesis techniques which are, each by itself, known in the art.

The vasoactivity assays and analyses are also well known and accepted in the art. In addition, the distinguishing details of the synthesis of the claimed compounds

and the practical performance of the activity assays are disclosed in the specification. One of skill in the art would have no difficulty in making, testing and using the presently claimed compounds as vasoactive agents.

Applicant contends that demonstrating a relatively simple yet novel rationale for designing NO-donating agents based on the above-mentioned chemical moieties, while not based on prior art, is providing tools and instructions for a skilled artisan of the field. The instant application presents a coherent and novel approach which adds an innovative concept to a greatly multifaceted filed, and this concept is well exemplified in a numerous examples, as stated by the Examiner.

Ample support, enablement and working examples demonstrating the preparation of such compounds and their activity as non-tolerance inducing NO-donating agents are provided throughout the instant application in various SAR studies on pages 143-151 of the instant application, as stated by the Examiner.

*The amount of direction provided by the inventor/Existence of working examples/The quantity of experimentation needed to make or use the invention:*

The Examiner alleged that the direction and working examples are limited to the making/using of compounds that have written description support, and that the direction/guidance is limited and cannot be extended to support the full scope of claim supra.

Applicant argues that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Applicant contends that the rational of the invention is exemplified and practiced with numerous examples. Applicants further contends that a comprehensive and extensive structure-activity relationship analysis of the results, spanning pages 143-151 and presenting detailed analyses of both the vasoactivity and the lack of tolerance emergence exhibited by the claimed compounds, is evidently provided.

Applicant further contends that this massive volume of work is presented in the instant application in order to demonstrate a general concept. Arriving at narrow conclusions with respect to an optimal agent would still require some testing and analysis, however it would not require the same amount of trials since the underlying concepts of designing, testing, identifying and arriving at an active agent is provided

in the instant application, hence reducing the scope of experimentation for anyone skilled in the art when practicing the invention without undue efforts.

Applicant therefore believes to have overcome the Examiner's rejection.

***35 U.S.C. § 112, Second Paragraph Rejections***

In one particular, the Examiner has stated that claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 has been amended.

Specifically, the Examiner has stated that the claim refers to Table 1 and Table 2, and that the claims must stand alone to define the invention and incorporation by express reference to specification and/or drawings is not permitted. The Examiner has further stated that one must refer back to the specification to determine what Applicant is claiming by the express reference to the tables, and suggested that Applicant insert the data from the appropriate tables into the claims.

Applicant has chosen, in order to more clearly define the claimed invention, to amend claim 32 so as to recite a list of compounds pertaining to the presently claimed subgenus which are encompassed by the instant application, using their chemical names as presented in Table 2.

Applicant believes to have overcome the Examiner's rejection.

In another particular, the Examiner has stated that claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been canceled, thereby rendering the Examiner's rejection moot.

***Additional amendments***

As delineated hereinabove, Applicant has chosen to cancel, without prejudice, claims 7, 12-15, 18-21, 24-27, 30 and 31.

***Related Applications***

To fully comply with requirements recently set forth under *McKesson Information Solutions Inc. v. Bridge Medical Inc.*, 487 F.3d 897 (Fed. Cir.2007), Applicant hereby identifies U.S. Patents Nos. 7,189,750, 7,332,513 as well as U.S.

Patent Application Nos. 20060183912, 20060069139, 20060183913 and 20060183718; which are co-filed National Phase applications deriving from PCT/IL05/00481 filed on May 5 2005, of which the instant application also derives.

Priority issues raised in the cases of U.S. Patent Application Nos. 11266/,346, 11/266,424 and 11/266,431 have been addressed hereinabove.

In addition, Applicant wishes to bring to the attention of the Examiner the art cited by the Examiner of 11/266,346, 11/266,424 and 11/266,431, namely Thatcher *et al.*, U.S. Patent Application having publication No. 2005/0137191 (also referred to herein as US 2005/0137191).

Applicant contends that, as argued hereinabove, since the claimed invention is fully supported by Provisional Patent Application No. 60/567,824, filed May 5, 2004, US 2005/0137191, which was filed September 17, 2004, should not be regarded as prior art with respect to the claimed invention.

US 2005/0137191 by Thatcher *et al.* is a continuation-in-part of U.S. Patent Application No. 10/147,808, which matured in the meantime into U.S. Patent No. 6,916,835, which is a division of U.S. Patent No. 6,310,052, which is a continuation-in-part of U.S. Patent No 5,883,122, which is a continuation-in-part of U.S. Patent No. 5,807,847. U.S. Patent Application having publication No. US 2005/0137191 is also a continuation-in-part of U.S. Patent Application No. 09/473,713, which matured in the meantime into U.S. Patent No. 7,115,661.

A detailed analysis set forth in response to the Examiner's rejections in corresponding cases, as identified hereinabove, shows that the claimed invention is neither anticipated by, nor rendered unpatentable over, Thatcher's U.S. Patent Nos. 5,807,847, 5,883,122, 6,310,051, 6,916,835 and 7,115,661, from which US 2005/0137191 claims priority.

Art other then US 2005/0137191 that was raised in the prosecution of the above-mentioned cases include Egli *et al.* (U.S. Patent No. 4,505,857) and Shiokawa *et al.* (U.S. Patent No. 4,923,886) in the case of the related U.S. Patent Application No. 11/266,431; and Shiokawa *et al.* and Garvey *et al.* (U.S. Patent No. 6,552,047) in the case of the related U.S. Patent Application No. 11/266,346.

Applicant contends that these documents fail to teach the subject matter described and claimed in the above-referenced applications.

In re Application of: Peter ASSAF et al
Serial No.: 10/555,664
Filed: November 4, 2005
Office Action Mailing Date: January 4, 2008

Examiner: Sun Jae Y. Loewe
Group Art Unit: 1626
Attorney Docket: 30724

In view of the above amendments and remarks it is respectfully submitted that amended claims 6, 17, 32, 33 and 65, and claims 66-75, are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: July 3, 2008

***Encl.:***
Petition for Extension (Three Months)